Integrative Methods

Integrative Genomics module

Michael Inouye
Centre for Systems Genomics
University of Melbourne, Australia

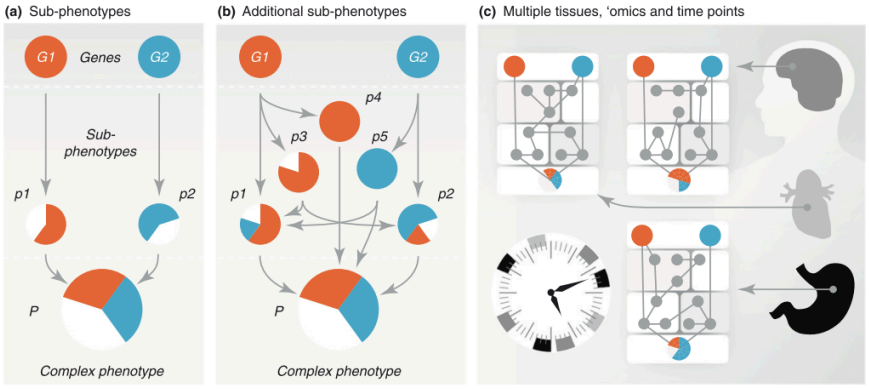
Summer Institute in Statistical Genetics 2016
Seattle, USA

@minouye271
inouyelab.org

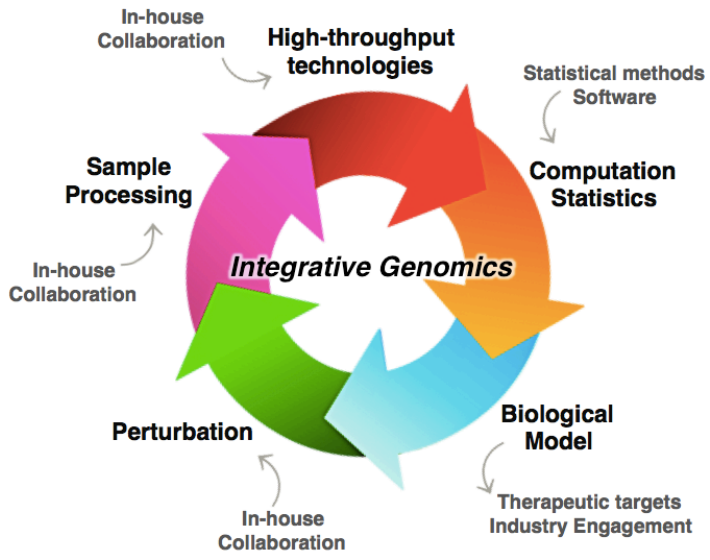
This lecture

- **Background**
- **Challenges**
- **Example: Gene co-expression networks in DILGOM cohort**
- **Example: Gene expression data to support genomics of metabolome**

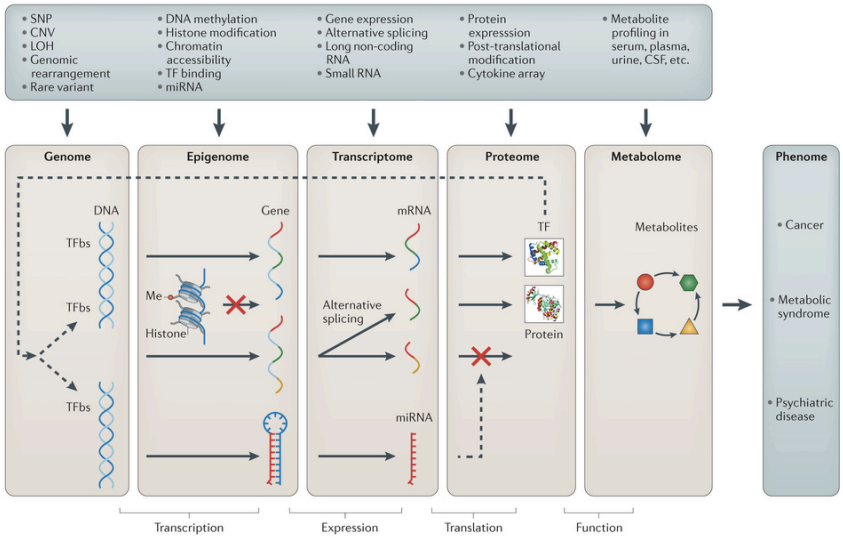
Background



Inouye, *Trends Genetics* 2011

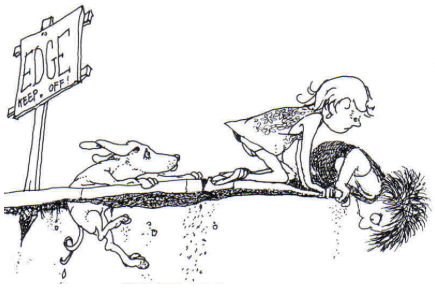


Multi-omics



Ritchie MD et al, *Nat Rev Genet* 2015

Where the sidewalk ends…



Integrative analysis is a relatively undeveloped area

Lots of scope for development and novel ideas

Nothing close to consensus on analytical approaches and strategies

Challenges

- **Large P: High dimensionality**
  - 10K, 100K, 10M variables per sample
- **Small N**
- **Heterogeneous data**
  - Different molecules
  - Different technologies
  - Different sampling strategies
- **Correlation**
- **Computational efficiency/feasibility**

Main things to be aware of

- **Understand the biological models underlying the data**
  - Context and interpretation
- **Know the technology**
  - Batches, biases, error profiles, sensitivities/specificities, missing data
- **Know the sampling strategy(s)**
  - Group-wise (case/control), population-based, enrichments, stimuli?
- **Spend time exploring the data**
  - Without exception, you will see things that require follow up
- **Build analysis pipelines and log all analyses**
- **The data may be complex but your analysis and presentation doesn't have to be**

Gene expression has a major role integrative analysis

- Insights into biomolecular networks
- Less technical variability than proteomics
- Relatively affordable
- Stable tissues are readily available
- Many network methods have been applied to gene expression data in the past
- Gene expression is thus a convenient way to characterise the average biological state of the cell population(s) being assessed

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An Immune Response Network Associated with Blood Lipid Levels

Michael Inouye[1,2¤*], Kaisa Silander[3], Eija Hamalainen[1], Veikko Salomaa[4], Kennet Harald[4], Pekka Jousilahti[4], Satu Männistö[4], Johan G. Eriksson[4,5,6,7,8], Janna Saarela[3,9], Samuli Ripatti[3], Markus Perola[3], Gert-Jan B. van Ommen[2], Marja-Riitta Taskinen[10], Aarno Palotie[1,3,11,12], Emmanouil T. Dermitzakis[1,13], Leena Peltonen[1,3,11†]

518 randomly sampled individuals (DILGOM)

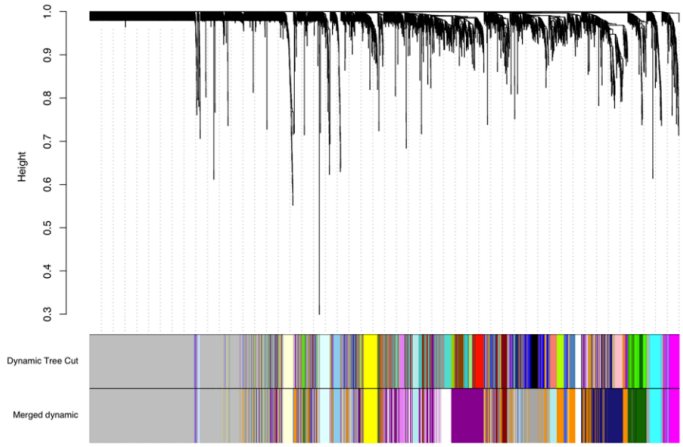
Fasting whole blood

Genome

Transcriptome

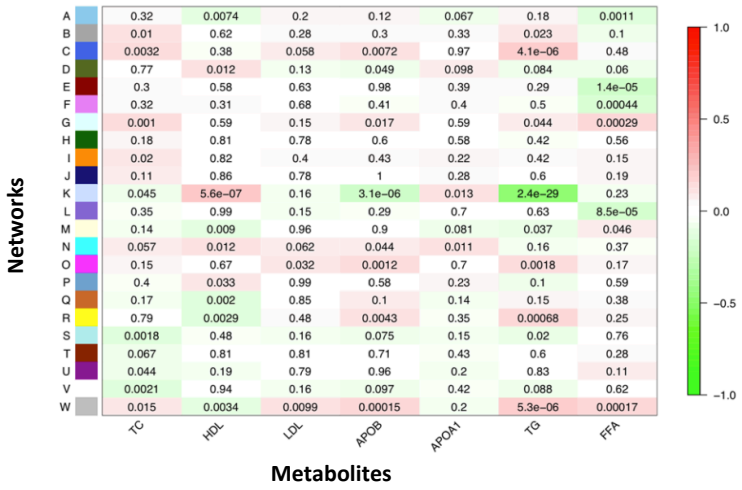
Metabolome

Identifying gene co-expression networks



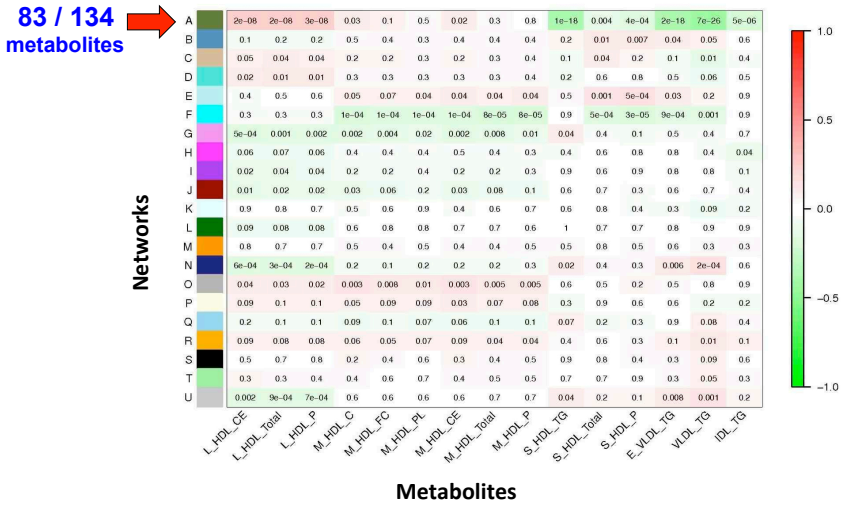
Inouye et al; *PLoS Genetics*, 2010

Networks and standard clinical lipid measures



Inouye et al; *PLoS Genetics*, 2010

Relationships between gene networks and metabolome



Inouye* & Kettunen* et al; *Molecular Systems Biology*, 2010

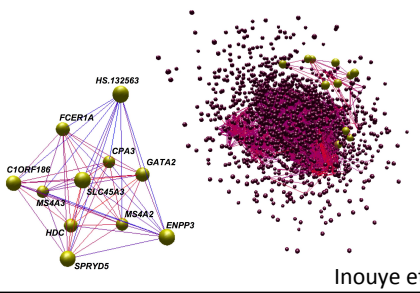
LL module appears to be involved in immune response

Genes

- ***FCER1A*** – high affinity IgE receptor
- ***MS4A2*** – high affinity IgE receptor
- ***HDC*** – enzyme for histamine synthesis
- ***CPA3*** – mast cell secreted peptidase
- ***GATA2*** – TF crucial for mast cell dev
- ***SLC45A3*** - *?*
- ***SPRYD5*** - *?*
- ***MS4A3*** - *?*
- ***ENPP3*** - *?*
- ***C1ORF186*** - *?*
- ***HS.132563*** - *?*

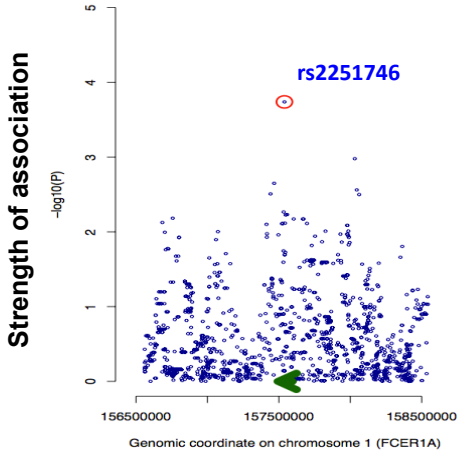
Immune markers

- IL-1ra (P=3.1x10^{-6})
- C-reactive protein (P=2.6x10^{-4})
- HMW adiponectin (P=1.6x10^{-5})
- Total IgE (P>0.05)



Inouye et al; *PLoS Genetics*, 2010

Does genetic variation influence LL module?



FCER1A $P = 1.83 \times 10^{-4}$
LL module $P = 4.28 \times 10^{-6}$

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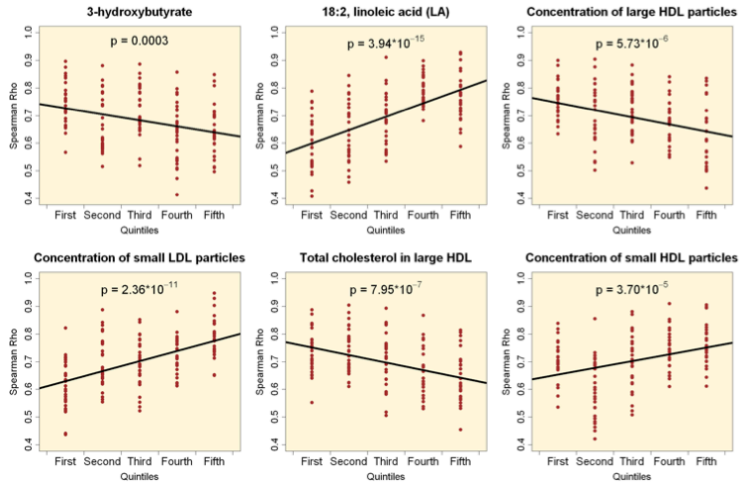
Genome-Wide Scan on Total Serum IgE Levels Identifies *FCER1A* as Novel Susceptibility Locus

Stephan Weidinger[1,2,3*], Christian Gieger[3,4*], Elke Rodriguez[2], Hansjörg Baurecht[2,5], Martin Mempel[1,2], Norman Klopp[3], Henning Gohlke[3], Stefan Wagenpfeil[3,6], Markus Ollert[1,7], Johannes Ring[1], Heidrun Behrendt[8], Joachim Heinrich[3], Natalija Novak[7], Thomas Bieber[7], Ursula Krämer[9], Dietrich Berdel[9], Andrea von Berg[9], Carl Peter Bauer[10], Olf Herbarth[11], Sibylle Koletzko[12], Holger Prokisch[13,14], Divya Mehta[13,14], Thomas Meitinger[13,14], Martin Depner[12], Erika von Mutius[12], Liming Liang[15], Miriam Moffatt[16], William Cookson[16], Michael Kabesch[12], H.-Erich Wichmann[3,4], Thomas Illig[3]

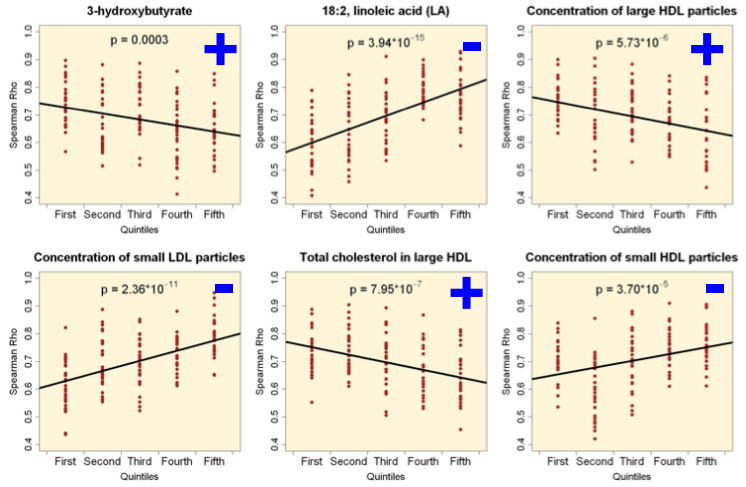
Inouye et al; *PLoS Genetics*, 2010

LL module appears reactive, do metabolites affect its connectivity?



Inouye* & Kettunen* et al; *Molecular Systems Biology*, 2010

Yes, it's a potential negative feedback loop



Inouye* & Kettunen* et al; *Molecular Systems Biology*, 2010

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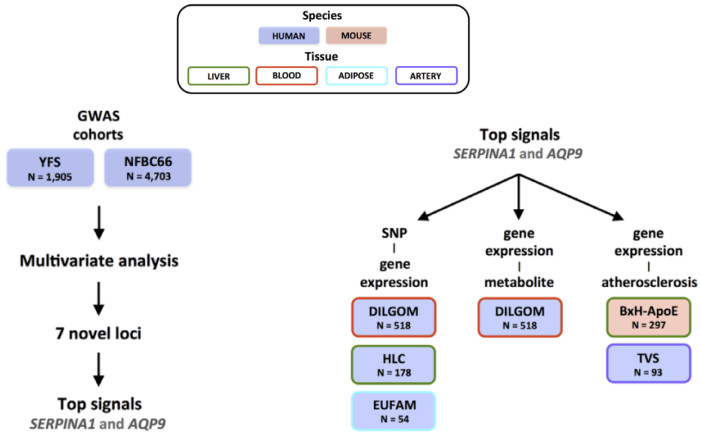
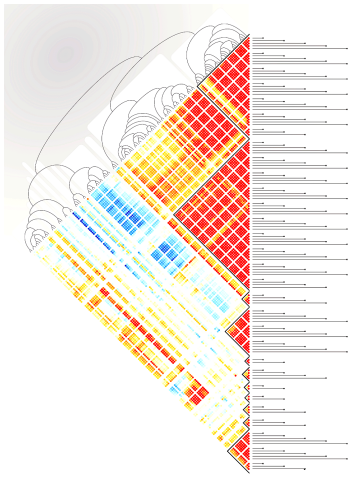
Novel Loci for Metabolic Networks and Multi-Tissue Expression Studies Reveal Genes for Atherosclerosis

Michael Inouye[1,2*], Samuli Ripatti[3,4,5], Johannes Kettunen[3,4], Leo-Pekka Lyytikäinen[6], Niku Oksala[6,7], Pirkka-Pekka Laurila[3,4,8], Antti J. Kangas[9], Pasi Soininen[9,10], Markku J. Savolainen[9,11,12], Jorma Viikari[13], Mika Kähönen[14], Markus Perola[4], Veikko Salomaa[4], Olli Raitakari[15], Terho Lehtimäki[6], Marja-Riitta Taskinen[16], Marjo-Riitta Järvelin[11,17,18], Mika Ala-Korpela[9,10,12,17], Aarno Palotie[3,5,8,19], Paul I. W. de Bakker[19,20,21,22]



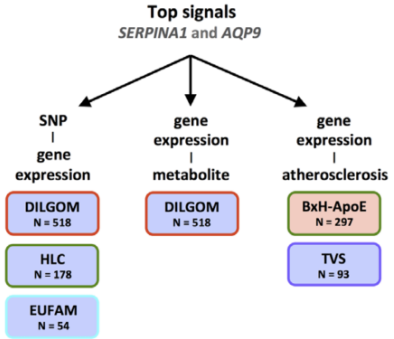
Determining metabolite networks



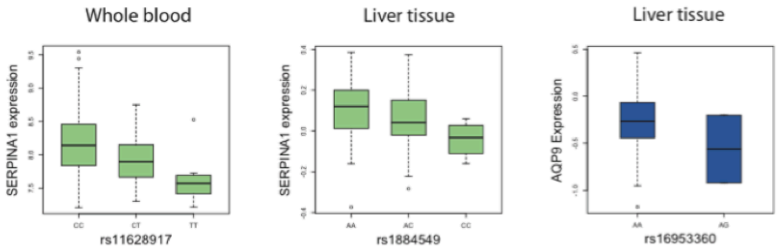
1 – apoB lipoproteins
2 – BC and aromatic amino acids large TG-rich VLDL
3 – large HDL
4 – small HDL
5 – polyunsaturated lipids
6 – ketone bodies
7 – glucose-alanine cycle
8 – renal function
9 – FA chain length/composition
10 – LDL diameter and FA composition
11 – urea & acetate

34 significant loci total 7 novel

Metabolite networks	Top SNP	Chr	Pos	Top Pvalue	Top metabolite	Gene
1,2	rs1303	14	93914596	5x10^-48	IDL-C	SERPINA1
1,2,3,4	rs16939881	15	56259271	3x10^-27	XL-HDL-TG	AQP9



SNPs for metabolic networks also drive *AQP9* and *SERPINA1* expression



DILGOM
N = 518
P < 10^-10
R^2 = 0.07

SNP associated with metabolic networks 1, 2

HLC
N = 178
P = 4x10^-3
R^2 = 0.04

SNP associated with metabolic networks 1

HLC
N = 178
P = 5x10^-3
R^2 = 0.04

SNP associated with metabolic networks 1,2,3,4

SERPINA1

Identification of genetic variants influencing the human plasma proteome

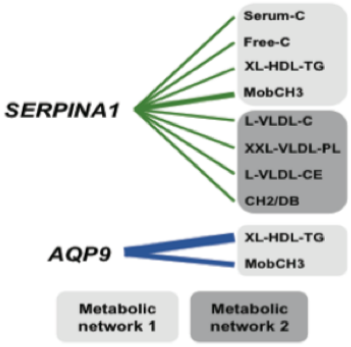
Åsa Johansson[a,b], Stefan Enroth[a], Magnus Palmblad[c], André M. Deelder[c], Jonas Bergquist[d], and Ulf Gyllensten[a,1]

[a]Department of Immunology, Genetics, and Pathology, Rudbeck Laboratory, SciLifeLab, Uppsala University, 75185 Uppsala, Sweden; [b]Uppsala Clinical Research Center, Uppsala University, 75237 Uppsala, Sweden; [c]Center for Proteomics and Metabolomics, Leiden University Medical Center, 2333 ZC, Leiden, The Netherlands; and [d]Department of Chemistry–Biomedical Centre, Analytical Chemistry, SciLifeLab, Uppsala University, 75124 Uppsala, Sweden

Edited* by Richard N. Zare, Stanford University, Stanford, CA, and approved February 11, 2013 (received for review October 8, 2012)

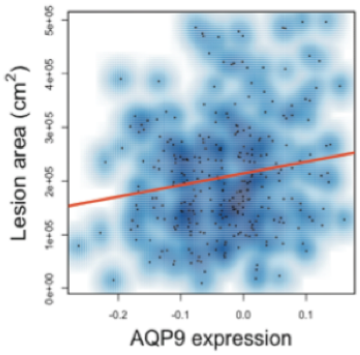
PNAS 2013

AQP9 and *SEPRINA1* expression is associated with metabolites



Metabolite	Chr	Position	Pvalue	Beta (95% CI)	Expressed Gene
XL-HDL-TG	15	56265176	8.48E-09	-0.61 (-0.82 - -0.41)	*AQP9*
MobCH3	15	56265176	7.16E-05	-0.43 (-0.63 - -0.22)	*AQP9*
MobCH3	14	93914570	6.46E-05	-0.51 (-0.75 - -0.26)	*SERPINA1*
L-VLDL-CE	14	93914570	2.47E-04	-0.49 (-0.76 - -0.23)	*SERPINA1*
XXL-VLDL-PL	14	93914570	2.48E-04	-0.51 (-0.78 - -0.24)	*SERPINA1*
L-VLDL-C	14	93914570	2.63E-04	-0.48 (-0.73 - -0.22)	*SERPINA1*
XL-HDL-TG	14	93924923	3.16E-04	-0.37 (-0.58 - -0.17)	*SERPINA1*
Free-C	14	93924923	3.98E-04	-0.37 (-0.57 - -0.16)	*SERPINA1*
Serum-C	14	93924923	4.00E-04	-0.37 (-0.57 - -0.17)	*SERPINA1*
CH2/DB	14	93924789	4.21E-04	1.14 (0.51 - 1.77)	*SERPINA1*

Liver *AQP9* associated with atherosclerosis in mouse model



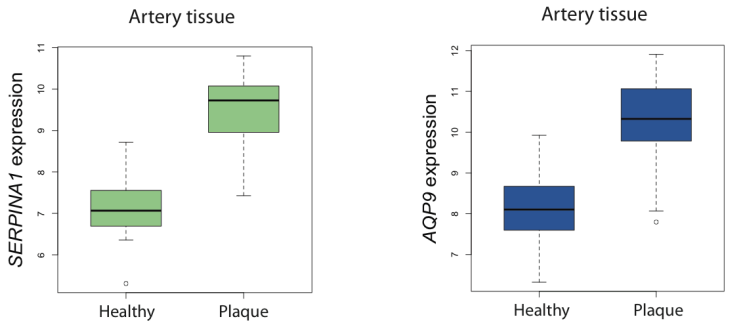
BxH-ApoE (N = 297):

- derived from backcross of highly susceptible to atherosclerosis (C57BL/6J *ApoE*$^{-/-}$) and highly resistant (C3H/HeJ *ApoE*$^{-/-}$).
- Fed on high-fat, western diet for 16 weeks then euthanized at 24 weeks.

***P* = 5x10^-3**

Samples in top decile of *AQP9* expression have on average 30% larger lesion area than those in bottom decile

AQP9 & *SERPINA1* in human aorta



Accessible resources for integrative genomics

- SageBase (via Sage BioNetworks)
- UK BioBank
- ImmGen
- ImmVar
- ENCODE
- THL Biobank
- TwinsUK
- iHMP / HMP2
- GTEx
- Epigenomics Roadmap Project
- Collaborative Cross (~outbred mice)
- Coming Soon: Precision Medicine Initiative